Articles

From Leningrad to the Day-Care Center
The Ubiquitous *Giardia lamblia*

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Giardiasis is recognized as a worldwide public health problem. Seroprevalence data from both the developing and developed world show high rates of carriage in populations at risk for fecal-oral transmission, such as children in day-care centers. Outbreak investigation has expanded our understanding of reservoirs for *Giardia lamblia* and of the routes of transmission. Various host factors have been associated with infection. The pathogenesis of giardial infections is being elucidated, in particular the role of lectin activation in producing disease. Three standard chemotherapeutic agents are available in the United States. The institution of community-wide prevention measures is equally important. Current areas of investigation including antigenic composition and enzymatic variants should result in effective forms of immunotherapy, while more effective forms of chemoprophylaxis could assist in eradicating the pathogen from institutional settings.

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A description of the pathogen responsible for giardiasis may be found in the works of Antony van Leeuwenhoek, who discovered in 1681:

> animalcules . . . all of the one and the same make; their bodies [are] somewhat longer than broad and their bellies [are] flatlike, furnished with sundry little paws, wherewith they made such a stir in the clear medium, and among the globules, that you might e'en fancy you saw a pissabed [woodlouse] running up against a wall; and albeit they made a quick motion with their paw, yet for all that they made but small progress.[1]

Such "animalcules," probably *Giardia lamblia,* were not subsequently described until a Bohemian physician, Wilhelm Lambl, ascribed to the organism its first scientific name, *Cercomonas intestinalis,* and elucidated its place in the ecosystem, including it among the fecal flora.[2] Western Europeans recognize his contribution in one of their two names for the pathogen: *Lamblia intestinalis*[3] or *Giardia intestinalis.* The term *Giardia* appears in discussions written by investigators from Berkeley, California, and Germany during the early 20th century; *Giardia* honors a French biologist named Alfred Giard. Hence, the name *Giardia lamblia* honors two 19th-century European scientists.[4,5]

With the modern growth in travel and increased attention to community epidemiology, the importance of *Giardia* species in human disease resurfaced. In the 1960s Americans returning from the Soviet Union with watery diarrhea carried the pathogen in stool; investigations pinpointed the water system in Leningrad.[6] A reported community-wide outbreak wherein *G lamblia* was incriminated occurred in Aspen in 1964-1965: protracted episodes of gastroenteritis developed among those who drank from the city water supply.[7] Such outbreak investigations have supplemented studies of antigenic composition, ultrastructure, life cycle, and enzyme variants in contributing to understanding *G lamblia* and giardiasis.

The Organism and Its Epidemiology

The life cycle of this flagellated protozoan is relatively simple: after cysts are ingested by a mammal, gastric acidity induces excystment and trophozoite development.[8] Trophozoites cause disease, although the mechanism by which disease occurs is debated. Organisms reencyst in the intestine on bile salt exposure[9] and excretion of cysts ensues, although cyst excretion does not have the strict disease dependence of trophozoite excretion, trophozoites being found only in diarrheic stools. The incubation period is usually between 7 and 15 days but may be much longer.[10] The trophozoites are very labile outside the host; cysts survive outside the host if not dehydrated or subjected to extreme temperatures.[11] The estimated infective dose in 50% of the population is between 10 and 100 cysts.[12]

Giardia species infections are ubiquitous. Outbreaks in the developed world have been reported from North America, Europe, and Australia[13-20]; in the developing world, high rates of endemicity have been found in Bangladesh,[21] Nigeria,[22] Guatemala,[23] and Peru.[24] The World Health Organization estimates that about 200 million infections occur annually in the developing world.[25]

In most communities the rate of endemic disease is unknown: giardiasis is often not reportable, variations exist in the methods of collecting specimens, and medical personnel vary in diagnostic skills. In the United States, 4% of stool specimens submitted to state health department laboratories are positive for *Giardia* species.[26] In one jurisdiction with required reporting, the incidence was 17.5 per 100,000 per year; 50% of cases occurred in day-care centers (SW Washington Health District, unpublished data, September 1985).

Community-wide outbreaks are typically from a common source. Although food and body fluids are recognized vehicles of transmission, water is the most common vehicle: the Public Health Service reports that 12 of 99 waterborne outbreaks during a four-year interval were due to *G lamblia.*[27,28] Camping-associated outbreaks are caused by ingesting contaminated water.[11,29] A community swimming pool-associated outbreak may have been due to a toddler soiling in the pool,[30] and a swimming slide-associated outbreak may have developed similarly.[31] Food outbreaks are uncommon; a Minnesota outbreak was associated with ingesting home-canned salmon prepared by an infected handler and served at a rural school[32]; a second in Connecticut was associated with cold noodle salad.[33]

Important community outbreaks include one in Camas, Washington (suburban Portland, Oregon), during 1976 that

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
IFA = indirect fluorescent antibody

affected 128 persons when the surface water supply broke down. Chlorinated and filtered water supplies failed to prevent the outbreak, and water treatment required flocculation, sedimentation, and coagulation.[13] A 1980 outbreak in Red Lodge, Montana, showed how climatic and environmental factors interact in producing disease. After the Mount Saint Helens (Washington) eruption, the deposit of volcanic ash that had been blown eastward, in conjunction with increased snowmelt associated with unusually warm weather, raised the city water supply level; the elevation provided animals access to surface water.[14] Ski resorts have been susceptible to *Giardia* species outbreaks, with reports from both Vail and Aspen, Colorado[7,15]; attack rates in Aspen were associated with the amount of water ingested and the length of residence—longer-term residents in 1981 had lower attack rates, ostensibly because of exposure during a 1964 outbreak.[15] A 1978 New England outbreak revealed the asymptomatic nature of many community-wide infections: 75% of those infected did not require treatment.[16]

Intercontinental travel and migration have been studied in East Germany: foreigners arriving from tropical areas showed higher rates of seroprevalence to *G lamblia* than did German travelers to and from the tropical areas, who had higher rates than German locals.[34] Other studies have outlined the high rates of giardiasis among immigrants from Third World countries.[35]

Well-substantiated methods of transmission also include sexual transmission and person-to-person. Three sexually transmitted disease centers have reported *G lamblia* among the fecal flora of homosexual and bisexual men.[36-38] In a case-control study, 18% of 126 homosexual men carried *Giardia* species, compared with 2% of inpatient and outpatient controls at New York Hospital.[39] Oral-anal sex, however, is not as established a predisposing factor toward giardiasis as it is toward amebiasis and helminthic infections.

Day-care center transmission has been substantiated in the United States, Canada, and Australia[40-45]; age-specific attack rates confirm that childhood disease maintains *Giardia* species in the community. In data from Houston, between 21% and 26% of 600 attendants at 30 day-care centers excreted *Giardia* cysts (trophozoite excretion between 3% and 4%).[40] Case-control methods have revealed that age-matched children not in day-care centers have lower isolation rates than those in day care: 2% versus 29% to 54%.[41] Australian investigators emphasize high rates of asymptomatic infection among children.[42] Family members and household contacts of infected children are at risk, secondary infection rates being between 17% and 47%.[40,42-45]

In summary, the epidemiology of *G lamblia* reveals that transmission occurs by many methods—common sources, sexual transmission, person-to-person nonsexual contact—but water is the usual source of community-wide outbreaks. Environmental factors that may be determinants of outbreaks include the presence of infected animals, the availability of surface water, and climate factors influencing the water supplies. A high prevalence of infection among toddlers and infants is a consequence of fecal-oral transmission in the developed world and water and food exposures in the developing world.

Host Risk Factors

The prevalence of giardiasis, as with any infection, is dependent on host, agent, and environmental factors. Environmental factors have been mentioned; agent factors will be discussed in another section. Host risk factors include sex- and age-specific attack rates. Males are infected more commonly than females.[46-51] Age-specific prevalence data show a propensity toward infection in childhood; the prevalence of infection in the younger-than-5 cohort ranges between 4% and 42% (Table 1).[21-23,46-54] The highest rates occurred in the Nile delta where among 2- to 4-year-old children, 42% showed cyst or trophozoite positivity, with excretion lasting as long as 17 weeks.[54] A difficulty establishing an association between infection and symptomatic illness is a common theme; studies from Peru report frequent reinfections after treatment.[24] Other possible host risk factors include immunodeficiency, human leukocyte antigen phenotype, nutrition status, achlorhydria, blood type, and concomitant infection with other agents, such as *Cryptosporidium* species or *Candida albicans*.

TABLE 1.—*Childhood Prevalence of* Giardia *Species Stool Carriage*

Population of Endemicity, Age	*Children, No.*	*Stool Specimens Examined, No.*	*Methods*	*Symptomatic, %*	*Prevalence, %*		*Reference Source*
					Childhood	*All Ages*	
Hawaiian school children	390	1	Wet mount	0	4-5	. .	Desowitz and Wiebenga, 1975[46]
Nîmes, France	. .	. .	. .	. .	> 6	. .	Fontaine et al, 1984[47]
Ontario day-care attendees, 2-5 years	244	1	Zinc sulfate	0	6-8	. .	Woo and Paterson, 1986[48]
Washington state infants, 1-3 years	518	1	FEA	. .	7.1*	. .	Harter et al, 1982[49]
Philadelphia inner-city children	385	. .	PVA-FE	. .	8-20	. .	Weiner et al, 1959[50]
Northwestern Australian children, 1-5 years	50	1	PVA-zinc sulfate	32†	12	4	Boreham and Phillips, 1986[51]
Nigerian children in endemic area, 1-5 years	449	1-3	FSE/iodine	. .	13.8	7	Oyerinde et al, 1977[22]
Rural Somalian children and mothers	517	1	Formalin/FE	. .	15-16	. .	Peltola et al, 1988[52]
Guatemalan children, 0-3 years	45	Weekly	PVA/FE/trichrome	0-8.2	20.2	. .	Farthing et al, 1986[23]
Costa Rican children younger than 5 years	293	1	. .	‡	25.3	. .	Moore et al, 1966[53]
Bangladeshi children younger than 5 years	91	. .	Iodine	. .	21-51§	. .	Gilman et al, 1985[21]
Rural Nile delta children, 2-4 years	42	Weekly	Trichrome	. .	42.4‖	17	Sullivan et al, 1988[54]

FE = formalin-ether, FEA = formalin-ethyl acetate, FSE = formol-saline-ether, PVA = polyvinyl alcohol

*21.3% among family member contacts.
†By history.
‡No difference in isolation rate was seen in the presence of diarrhea.
§Seroprevalence is higher among malnourished patients.
‖Cysts and trophozoites.

A variety of immunodeficient states—common, variable; Bruton's; the acquired immunodeficiency syndrome (AIDS)—have been studied with respect to giardiasis.[55,56] Persons with immunodeficiencies may not be at particular risk for severe giardiasis developing.[57-59] X-linked (Bruton's) agammaglobulinemia is not associated with a notable predisposition toward any gastrointestinal illness.[58] A workup for immunodeficiency is not indicated in patients with giardiasis.[60]

HLA phenotypes—A1/A2 and B12/B27—occur with a higher than expected frequency in patients with giardiasis.[61] T-cell deficiencies in animals are not necessarily risk factors; certain strains of mice are more susceptible to *Giardia muris* infections, however, as are congenitally athymic animals.[59] In humans the relationship is less clear. With AIDS, for example, the relationship is complex. A history of giardiasis is associated among homosexual men with an odds ratio of over 10 with the development of seropositivity to the human immunodeficiency virus and AIDS.[62] The incidence of giardiasis among uninfected AIDS patients appears not to be increased, however; homosexual AIDS patients with giardiasis have lower antibody levels than do heterosexual patients with giardiasis—but higher than healthy persons.[63]

Malnutrition is a likely risk factor for giardiasis, although the cause-and-effect relationship between the two is hard to clarify. In Bangladesh 57% of a malnourished cohort aged 1 to 5 was infected with *G lamblia*.[64] A Guatemalan study found, among infected infants, reductions in weight gain (but not height) during the second year of life.[23] A Zimbabwean study also correlated infection with *Giardia* species with indices of malnutrition including wasting and stunted growth.[65] The extent to which immunodeficiency is a significant predisposing cofactor in malnourished patients is unknown.

Persons with blood group A appear to be prone to the recurrence of giardiasis.[66] This is thought to be related to the antigenic similarities between blood group antigens and *Giardia* species: the organism does not evoke the same immunologic reaction it would if the blood group's glycoproteins differed. Data from Finland showed no correlation between blood groups and (nonrecurrent) giardiasis.[67] An association between giardiasis and achlorhydria has also been postulated,[67] although it is essential to control for blood groups because the A blood group is more common among achlorhydric patients.[68] Cystic fibrosis may be a risk factor: a case-control study (using household family members of cystic fibrosis cases as controls) reported higher infection rates among the patients with cystic fibrosis.[69]

In summary, major host risk factors associated with giardiasis are age and perhaps immunodeficiency. Concomitant infectious diseases may reflect acquisition from a common source. Immunotype, blood type, and achlorhydria share a minor role in contributing a propensity toward infection.

Clinical Symptoms

Most giardial infections, particularly those of infancy, are well tolerated and asymptomatic. When overt illness occurs, the spectrum is wide and ranges from an acute, mild, self-limited gastroenteritis to a protracted (the average duration of diarrhea in one Aspen outbreak was 44 days[7]) and debilitated malabsorptive state due to chronic gastroenteritis.[70-75] Frequent symptoms that accompany the gastroenteritis are fatigue, weight loss, abdominal cramps, nausea, and greasy stools.[6] In children malaise, dyspeptic disorders, and a failure to thrive may be due to giardiasis, and in adults symptoms may include a diminished capacity for work.[26] In the developing world, more than 40% of symptomatic infections last between four and six weeks.[23] The relative proportions of symptomatic and asymptomatic infections in areas with high endemicity are unknown (one study in an outbreak setting[16] documented a high rate of asymptomatic infection).

The small intestine, while the most common, is not the only site of disease. Malabsorptive complications associated with giardial infections include vitamin B_{12} deficiency due to nutrient competition,[76] iron deficiency due to impaired absorption,[77] and hypovitaminosis A.[78] Less common, documented complications (typically, case reports) include cholecystitis and mechanical jaundice as well as pancreatitis, upper gastrointestinal bleeding, and mesenteric adenitis.[79-81] Erythema nodosum has been associated with giardiasis,[82] as have ocular inflammation (iridocyclitis, retinal disease),[83] arthritis,[84] and even psychiatric manifestations in childhood.[85] Chronic urticaria is reported to occur with giardiasis and subsides with treatment of the infection; the basis is thought to be mucosal injury with the absorption of toxic materials.[86] Immunoglobulin E levels do not increase in giardiasis.[87]

Pathogenesis

There is no one accepted theory about how *G lamblia* causes disease. Pathologic findings vary but include blunting of small intestinal villi, lymphocytic infiltration, and occasional ulcerations[88-90] and do not correlate well with the disease state.[91] Postulated theories regarding pathogenesis include mechanical obstruction by giardial cysts; mucosal damage by nonmechanical means, toxic or metabolic (a metabolic example is the induction of brush border enzyme deficiencies); and deconjugation of bile salts, either by bacterial overgrowth or by giardial organisms.[59,92] Mucosal invasion is well documented histologically.[93] Indian studies have shown that the size of the inoculum of *Giardia* organisms has no effect, over a twofold log range, on either glucose or amino acid transport in intestinal brush border membrane vesicles of infected mice; hence, mechanical obstruction may not be a primary factor in pathogenesis.[94] In another study, brush border enzyme deficiencies, especially disaccharidase deficiencies, were prominent in a dexamethasone-immunosuppressed mice model.[95] Not all humans show mucosal damage, and enzyme deficiencies may be a consequence rather than a cause of mucosal disturbances. Bacterial overgrowth is also an inconstant finding.[92]

The importance of surface lectins has recently been delineated: *G lamblia* produces a lectin activated by human duodenal secretions (a duodenal protease) and inhibited by trypsin inhibitors. The lectin is inhibited competitively by mannose-6-phosphate and agglutinates to the same site in the duodenum where *G lamblia* attaches. The mechanism of lectin-induced organism attachment and resultant disease is unknown. This system is considered analogous to myxovirus activation by proteolytic cleavage of surface viral glycoproteins or the enhancement of *Trypanosoma cruzi* infections by the proteolysis of its surface membrane proteins.[96]

Serum antibodies against a major 82,000-dalton antigen of *Giardia* trophozoites are present among persons with persistent giardiasis.[97] Substantial indirect fluorescent antibody (IFA) titers have been detected in more than 85% of a Scandinavian adult population, with a fall in titers with treatment.[98] Indirect fluorescent antibody titers were present as long as 18 months in chronically infected persons in a study from Cincinnati; Indochinese refugees and male

homosexuals with AIDS had higher antibody levels than the uninfected.[63] Much of the detected antibody response in populations with high seroprevalence may be due to cross-reaction with other immunogens.[98] High concentrations of anti-*Giardia* antibodies have also been found in the breast milk of mothers in Bangladesh[64]; these antibodies may act in conjunction with free fatty acids of milk because fatty acids are known to be lethal to both *Giardia* cysts and other parasites.[99,100]

Ultrastructural studies have elucidated *Giardia* species motility and attachment.[101-103] The trophozoite attaches to the mucosa with a ventral disc whose ultrastructure consists of multiple microtubules, the outer surface of which contains bridges from which emanate microribbons. Motility is achieved by flagellae whose placement determines the direction of movement: posterior flagellae clear a concave space on the undersurface of the organism for purposes of attachment while caudal flagellae alter the movement of substances within the cytoplasm. Flagellae emerge from axonemes, organelles consisting, like the ventral disc, of microtubules but arranged in a geometrically constant pattern: nine peripheral pairs about two central pairs. Organelles degrade on encystation of the organism. The discovery that chitin is a structural component of cysts[104] suggests a possible therapeutic intervention with chitinases.

Diagnosis

A diagnostic workup includes the collection of several stool specimens—typically three—in polyvinyl alcohol fixative (vials should be given to patients with instructions to take them to a laboratory as soon as possible) followed by the identification of trophozoites or cysts by experienced laboratory personnel.[105] A small bowel biopsy or duodenal aspiration facilitates establishing the diagnosis. Combining stool cultures and duodenal aspiration is especially effective in diagnosis,[106] although the string test (Entero-test; Health Development Corporation) may be preferable. A string embedded in a gel capsule is swallowed, with the proximal end of the string taped to the face; the string is removed three to four hours later, when ostensibly it has reached the terminal duodenum; the distal section should contain bile-stained mucus in which motile trophozoites can be detected.[107,108] An intravenous secretin challenge increases the yield of organisms.[109] A stool enzyme-linked immunosorbent assay is currently available, is 92% to 98% sensitive, nearly 100% specific, and inexpensive; it may eventually replace multiple stool specimens and duodenal aspiration [110] and enable a diagnosis using a minimum of technology in a short interval (less than three hours).[111] Serum IFA levels are commonly present in patients with chronic infection,[63,98] although the correlation between antibody levels and stool specimen positivity in one malnourished cohort was poor.[112] A serum ELISA using cyst antigens has been developed[113] that has high sensitivity (91/92 asymptomatic carriers detected), but specificity is poor (cross-reactivity to heterologous parasitic antigens occurred).

Treatment

Approaches to therapy should consider both the individual and the community: Are individual cases associated with an outbreak? Are physicians receiving current recommendations during an outbreak? It should first be recognized that many infections clear in the absence of treatment.[73,114] The two most popular agents are nitroimidazoles and quinacrine. The nitroimidazoles include metronidazole, tinidazole, ornidazole, and nimorazole (only the first is marketed in the United States). They are effectively given as a single dose (500 mg),[26] although it is generally recommended that metronidazole be given over a seven- to ten-day course at 500 to 750 mg per day in two to three doses.[107,115-122] A major concern with metronidazole use is mutagenicity and carcinogenicity. Its use is usually well tolerated, although patients should be reminded of disulfiram-like effects—which may occur as late as 48 hours after therapy—when taken in conjunction with alcohol. Less commonly reported symptoms include headaches, an unpleasant taste in the mouth, stomatitis, paresthesias, dizziness, and transient neutropenia.[116] Quinacrine is cheaper, but side effects that may limit compliance[119] include gastrointestinal disturbances, blood dyscrasias, urticaria, exfoliative dermatitis, yellowing of the skin, and ocular toxicity; toxic psychoses may occur in 1% to 2% of patients,[123] and hepatic necrosis is rare. Furazolidone is another alternative. A liquid form is well tolerated by children,[124] but gastrointestinal side effects occur, hemolysis may occur in those with a glucose-6-phosphate dehydrogenase deficiency, and it is carcinogenic in animals[119]; the optimal course appears to be ten days.[125] The relative efficacy of the compounds is debatable (none of the agents cure more than 85% of cases), and both metronidazole[26,118,120] and quinacrine[126] have their strong advocates. In an in vitro system using thymidine incorporation, the relative killing efficacy of nitroimidazoles is greater than that of furazolidone, which is greater than that of quinacrine.[127] The World Health Organization currently recommends using nitroimidazoles.[26]

The management of severe cases during pregnancy is problematic; no agent is recommended during early pregnancy. The safety of metronidazole use in children and pregnant women is debatable[107,121]; while some investigators consider it safe to use during pregnancy,[116] in the first trimester its use should be restricted.[117,118] In a recent study of intestinal parasite carriage, including *Giardia* species, among 147 pregnant Thai refugees, there were no complications associated with the parasite infections. The authors consequently advocated withholding all antiparasitic chemotherapy during pregnancy.[128] On delivery, a concern with immediate treatment using metronidazole is its passage into breast milk.[107,129]

Community therapy is directed toward prevention.[13-17] Water sources of *Giardia* species are typically surface water; contaminated water requires either hyperchlorination or the combined methods of coagulation, sedimentation, and flocculation.[13] Filtration alone is insufficient, and chlorination alone requires levels of 2 to 5 mg per liter, levels that make water unpalatable. Boiling cyst-infected water immediately destroys the capacity to excyst.[11] Ozone has potential promise as an inactivating agent.[130] For hikers and campers who use limited quantities of water, iodination is sufficient,[29] although tetraglycine hydroperiodide is safer and easier to use than crystalline iodine.[131]

The proper treatment of institutional outbreaks is controversial.[40,132] It is often recommended that no treatment be given because such infections are usually well tolerated and control measures are hard to execute. Institutional asymptomatic infections, however, may be the source of more insidious or severe infections in the community. Immunoprophylaxis is not available, and chemoprophylaxis will become feasible only with the availability of cheaper, safer medications.

New Areas for Investigations

Topics currently being investigated that should assist in understanding *Giardia* species and its epidemiology include

protozoal enzymes and analyses of zymodenes (the patterns of isoenzyme variation),[133] morphometric observations,[134] animal reservoirs,[26] and antigenic characteristics.[135,136]

Antigenic characteristics assist in the development of serologic assays and immunotherapy.[135] Antigenic variation among organisms is known to occur both in vitro and in vivo, although the biologic significance of such variation is unknown.[135,136] In a recent review of vaccine developments, *G lamblia* was listed among the pathogens for which vaccines are unlikely to be developed in the next decade.[137] Although much work has been produced in the developing world,* there exists a need for epidemiologic studies outlining different modes of spread in the developed versus the developing world.[139] Other epidemiologic and therapeutic studies are needed to refine the role and assess the feasibility of eradicating infection in day-care centers among asymptomatic cyst passers—who are well recognized to maintain the disease.[40-45]

Additional studies on pathogenesis will delineate how lectin activation induces disease,[96] the primary versus the secondary role of brush border enzyme deficiencies,[95] structural-physiologic correlates of the organelles,[101-103] and the role of chitin in the disease.[104] Improved, available diagnostic assays are needed, in particular immunodiagnostic techniques that can establish the diagnosis using either serum or stool specimens.[110,111] Newer forms of chemotherapy are needed as well as assessments of nitroimidazole derivatives,[116,120,121] confirming reported cure rates of more than 90%.[122] The role of the immune system needs to be clarified as well. Further studies delineating the role of the immune system are also needed.

In summary, although *Giardia* species has been a neglected organism with poorly understood pathogenic potential, it is now considered an important cause of gastroenteritis as a consequence of contaminated water and food or venereal exposures. In day-care centers, person-to-person spread is common and asymptomatic cyst passers maintain disease. Periodic major waterborne outbreaks are controlled when attention is directed toward water delivery systems. Current areas for study include parasitic enzymes and antigenic characteristics, relationships to states of impaired immunity, new agents to manage community-acquired (including day-care centers) cases, and ranges of animal reservoirs. The development of safe, effective chemoprophylaxis and immunoprophylaxis should improve the control of giardiasis.

*References 21-23, 52-54, 64, 65, 78, 94, 95, 109, 120, 122, 128, 133, 138.

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